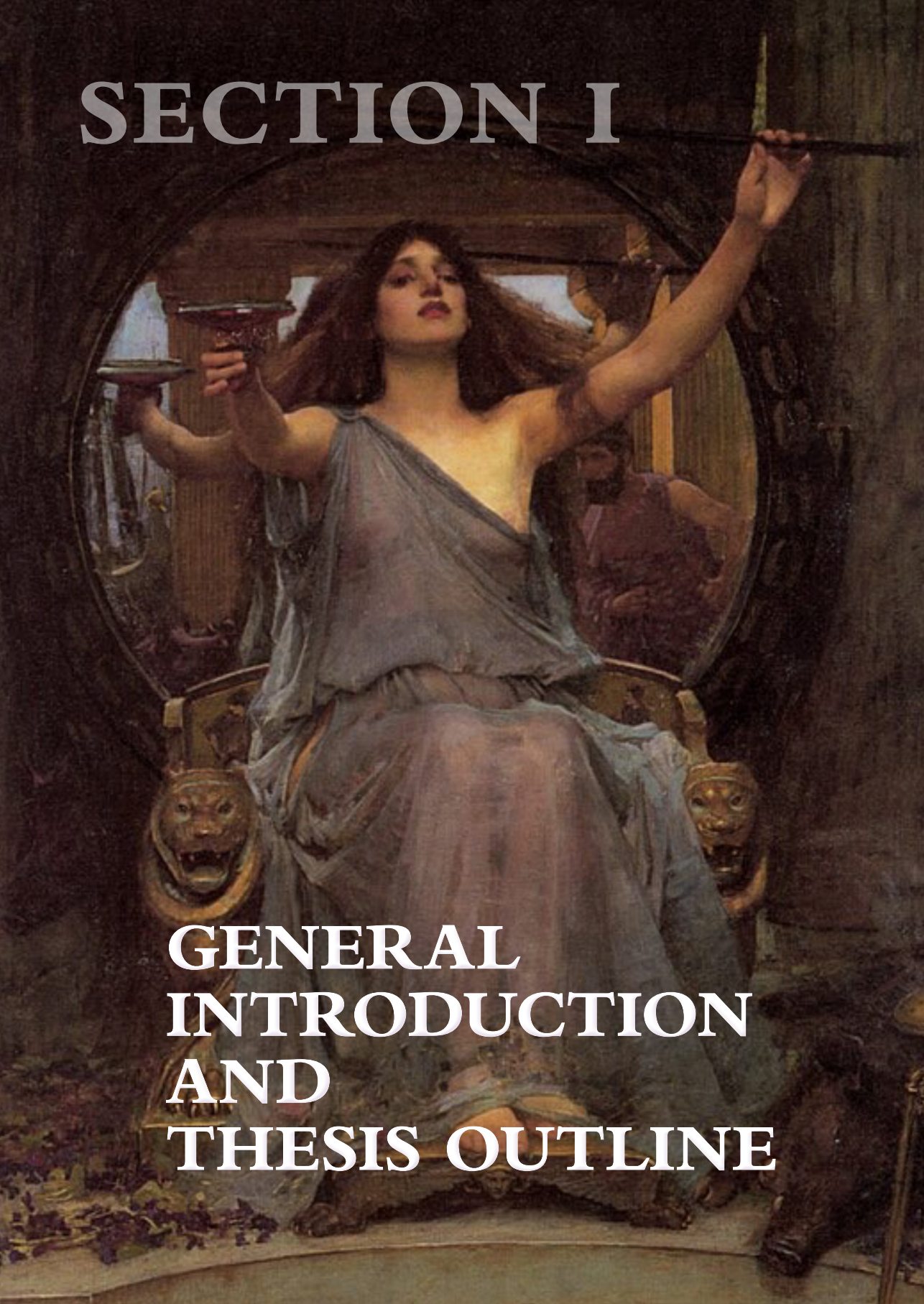
Diagnosis, differentiation and prevention in pancreatic diseases

Engels, M.M.L.

SECTION I



GENERAL INTRODUCTION AND THESIS OUTLINE

John William Waterhouse - Circe Offering the Cup to Ulysses (1891)

CHAPTER 1 - INTRODUCTION

INTRODUCTION

The content of this thesis transverses the landscape of pancreatic diseases and touches on the common bile duct due to its close anatomical relation to the pancreas. In the introduction of this thesis, first the relevant anatomy and physiology of the pancreas will be addressed. Subsequently, descriptions of the epidemiology and pathophysiology of the various pancreaticobiliary diseases covered will be given with the diagnostic and prevention difficulties currently encountered for each disease entity. This chapter will concede with how those challenges have led to the research questions outlined in this thesis.

PANCREAS

ANATOMY

The pancreas is located in the retroperitoneum and can be divided into the anatomical regions of head, body and tail (caput, corpus and cauda). The head is attached to the duodenum and subsequently crosses over towards the spleen where the tail lies (**Figure 1**). As compared to other solid organs, the pancreas has a variable anatomical appearance in different persons. The pancreas consists of three different cell types; Islet of Langerhans, acinar and ductal. [1] The pancreatic ductal system transports pancreatic juice into the duodenum, and consists of the main pancreatic duct, accessory duct of Santorini and side branches of the main ductal system.

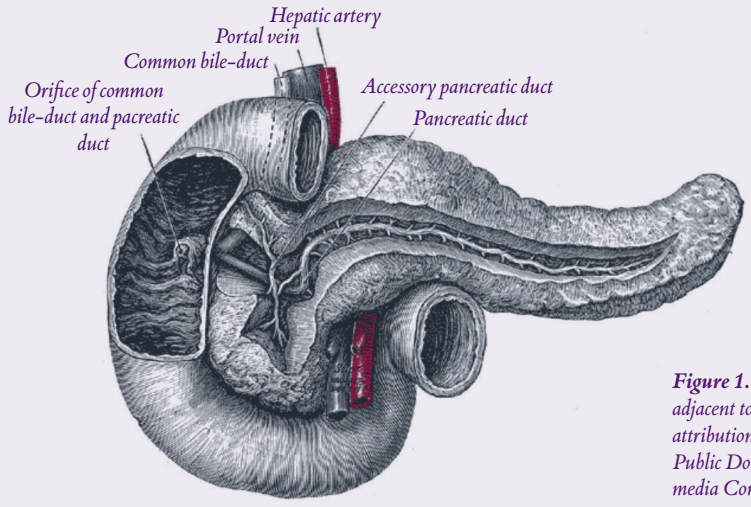


Figure 1. *The pancreas, situated adjacent to the duodenum. Image attribution: Henry Vandyke Carter, Public Domain, accessed via Wikimedia Commons*

PHYSIOLOGY

The pancreas possesses both an endocrine and exocrine function. The endocrine function is responsible for glucose homeostasis in the body [2, 3] with Islet of Langerhans cells producing glucagon (alpha cells) and insulin (beta cells). The exocrine function of the pancreas is performed by acinar cells lining the ductal system. These produce various pancreatic enzymes for digestion of nutritious components including amylase (starches), lipase (fat) and proteases, including trypsin and chymotrypsin (protein), as demonstrated in seminal work by Bernard and Pavlov independently in the late 19th century. [4, 5] Pancreatic enzymes, combined with alkaline bicarbonate to neutralize stomach acid, produced by the ductal cells, form the basis of pancreatic juice. It's secretion can be stimulated in various ways, including hormonal influence by cholecystokinin (formally known as pancreozymin) on the acinar cells, [6] the influence of secretin on the ductal cells, [7] stimulation of the vagal nerve, [4] and the presence of food in the upper gastrointestinal tract. [4]

PANCREATIC DUCTAL ADENOCARCINOMA AND PRECURSOR LESIONS

EPIDEMIOLOGY

The incidence of pancreatic cancer is relatively low at 13 per 100.000 person years,[8] with a meager 5-year survival of 13%.[9] Non-specific symptomology combined with quick metastasizing biology and lack of effective systemic treatment options (due to the tumors inherent cold immunity properties) further contribute towards PDAC's high mortality, [10] leading to its projected ascent from 3rd to 2nd leading cause of cancer death well before 2030. [11, 12] Risk factors for developing pancreatic cancer include cigarette smoking, heavy alcohol consumption, long-standing diabetes mellitus, obesity, chronic pancreatitis and hereditable genetic mutations. [10, 13]

PATHOPHYSIOLOGY

More than 90% of pancreatic cancers are of the pathological subtype pancreatic ductal adenocarcinoma (PDAC). [14, 15] PDAC arises from ductal epithelia and is surrounded by dense fibrous stoma. [16] Genetic mutations accumulate in precursor lesions causing progressive dysplasia and eventually the development of carcinoma in situ. [17] Pancreatic intraepithelial neoplasia (PanIn) is the most common precursor for PDAC and is microscopic in origin. [18] Intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) are macroscopic cystic pre-cursor lesions with varying grades of dysplasia that can develop into invasive pancreatic cancer, [19, 20] and therefore are eligible for imaging surveillance. [21, 22] While the genetic marker KRAS is present in an overwhelming majority of pancreatic cancers, [23-25] and in the majority of low grade dysplastic pre-cursors, [26] high risk genetic mutations associated with high grade dysplasia (HGD) and cancer development are heterogenous, including *TP53*, *SMAD4* and *CDKN2A* at the highest frequency of ~50%.[23] Additionally, alterations in DNA-methylation have shown promise in differentiating between pancreatic cancer and chronic pancreatitis. [27]

DIAGNOSTIC IMAGING

The optimal imaging modality in pancreatic cancer depends on the goal at hand. A dual-phase contrast enhanced computed tomography (CT) is most informative and available in the diagnostic phase, if there is a clinical suspicion of pancreatic carcinoma. [28] The exception is when patients are enrolled in a surveillance program for high-risk individuals. For this cohort, magnetic resonance imaging (MRI) is preferential as sequential radiation exposure from CT is avoided, [29, 30] and it is better suited for the detection and characterization of small and/or isodense lesions, [31] which can be missed on CT. Some screening programs are endoscopic ultrasound (EUS) based. [32] Once there is a suspicion of pancreatic cancer, patients will undergo an EUS as this allows for simultaneous tissue acquisition. [33] In surgical candidates, an MRI or positron emission tomography-CT (PET-CT) will be performed to rule out small liver metastases. [28, 34]

EARLY DETECTION CHALLENGES

Efforts are underway to define high-risk (enriched) populations in which surveillance would be a justified strategy for detecting early-stage cancer (**Figure 2**). [35] For populations at the highest risk, such as individuals with a *CDKN2A* p-16 mutation, survival benefits of surveillance have been demonstrated. [36] Prior to the expansion of screening/surveillance efforts to include other at-risk populations with a lower lifetime risk, there is a need to improve the diagnostic modalities used to screen these populations. Early-stage cancers <2cm that are associated with greater survival are hard to detect on cross-sectional imaging, [37, 38] and there are currently no biomarkers other than CA19.9 that have found widespread clinical implementation. There are still instances of interval cancers in which inoperable cancers are found between screening moments, [39, 40] or late stage tumor detection with early nodal involvement despite frequent imaging. [41, 42] Furthermore, obtaining tissue samples by endoscopic ultrasound guided fine-needle-aspiration (EUS-FNA) of areas suspect for cancer can come at a risk of adverse events[43], albeit lower than the risk associated with resolving malignant biliary obstruction by endoscopic retrograde cholangiopancreatography (ERCP), [44] as elaborated upon in the next section.

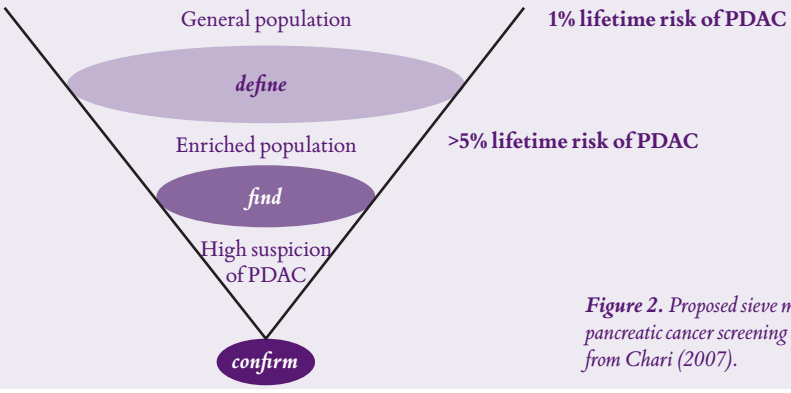


Figure 2. *Proposed sieve model for pancreatic cancer screening as adapted from Chari (2007).*

POST-ERCP PANCREATITIS

EPIDEMIOLOGY

The ERCP is an interventional endoscopic procedure for alleviating benign or malignant obstruction of the common bile or pancreatic ducts. The most common indication for an ERCP is choledocholithiasis: the presence of gallstones in the common bile duct.[45] ERCPs are not without risk, approximately 10% of the procedures result in pancreatitis.[44]

PATHOPHYSIOLOGY

The pathophysiology of post-ERCP pancreatitis is multifactorial.[46] First, local trauma from extensive manipulation causes edema at the pancreatic duct orifice,[47] leading to mechanical obstruction of pancreatic juice outflow and pre-emptive activation of pancreatic enzymes. Therefore, pancreatic duct (PD) stents have been the standard of reducing the risk of post-ERCP pancreatitis for over 20 years for high-risk patients (eg. after ampullectomy) and upon multiple inadvertent PD cannulation.[48,49] Second, in animal models, regional hypoperfusion has been shown to lead to pancreatic necrosis and pancreatitis,[50] which led to the pilot study on intravenous hyperhydration with Lactated Ringer's as a potential prophylaxis.[51] Finally, after various animal and in vitro studies on the contributory effect of inflammatory mediators, including prostaglandin synthesis and phospholipase-A2,[52,53] the use of non-steroidal anti-inflammatory drugs (NSAIDs) was proposed and received widespread implementation after the 2012 trial by Elmunzer et al.[54]

STRATIFICATION & PREVENTION CHALLENGES

Various challenges in preventing post-ERCP pancreatitis still remain. Whilst certain attributes concerning the patient, the procedure or the endoscopist convey a higher risk,[49] consensus surrounding the exact definition of a high-risk patient is lacking. This complicates decision making in which patients a prolonged post-procedural observation for adverse events is warranted. Furthermore, despite the aforementioned strong evidence on the benefit of various prophylactic measures, their use may vary amongst different practices and practitioners. Finally, due to the improvement of imaging modalities resolution in magnetic resonance cholangiopancreatography (MRCP) and EUS and the inherent risks procedural risks, an ERCP has evolved from a diagnostic procedure to one that should be solely indicated for therapeutic benefits. It is therefore essential to focus on how to eliminate ERCPs performed without therapeutic necessity, such as in the suspicion of choledocholithiasis when there are no common bile duct stones present upon examination.

THESIS OUTLINE AND AIMS

SECTION I: GENERAL INTRODUCTION

Section I contains the General introduction and thesis outline currently being read.

SECTION II: IMAGING AND ARTIFICIAL INTELLIGENCE

In section II, the focus lies on the appearance of pancreatic cancer on cross-sectional imaging in the (pre-)diagnostic stage, and potential innovations to improve the detection of early-stage cancer. In **chapter 2**, the aim is to characterize imaging findings of pancreatic cancer in a cohort of patients who underwent cross-sectional imaging prior to diagnosis, matched with age & gender matched controls. Retrospectively, two blinded radiologists assess whether abnormal imaging characteristics, suggestive of pancreatic cancer, were present. Once unblinded, they will assess what the potential cause for such errors could be using the RADPEER score. [55]

The results of the this chapter form the rational for investigating whether artificial intelligence could potentially improve early-pancreatic cancer detection by acting as a second reader/red flag system, mitigating human errors. In **chapter 3**, an overview is given of current artificial intelligence (AI) applications within the field of gastroenterology. Essential for algorithm development is the accruement of large quantities of high-quality, annotated data, which is a time-costly venture requiring expert knowledge. In **chapter 4**, the aim is to lay a groundwork for efficient data annotation necessary in the development of pancreatic cancer detection algorithms.

SECTION III: BIOMARKERS

In section III, the focus lies on the validation of biomarkers for two pancreatic diseases. As previously stated, the majority of pancreatic cancers are pancreatic ductal adenocarcinoma. Through its ductal origin, it is biologically plausible that genetic aberrations associated with PDAC can be found in pancreatic juice secreted from the ductal system. In **chapter 5**, the aim is to validate a panel of methylated DNA markers (MDM) for the detection of pancreatic cancer by combining a previously established 3-MDM panel with the clinically utilized biomarker CA19.9 in a prospective, multi-center cohort.

In the subsequent chapter the topic pivots to the early diagnosis of post-ERCP pancreatitis. Currently, there is no consensus over what exactly classifies a 'high-risk patient', and who should be eligible for longer post-procedural observation with a one-night hospital stay. The European Society for Gastroeintestinal Endoscopy (ESGE) guidelines recommend invasive serum amylase or lipase measurement, and if non-elevated, patients can safely be discharged. [49] The measurement of trypsinogen-2, in a point-of-care urine test, has been proposed as a non-invasive alterna-

tive.[56] In **chapter 6**, it will be investigated whether a combination of this urine trypsinogen-2 (UT-2) test with a patient and procedural risk factor based discharge tool[57] can predict safe same-day discharge in patients undergoing ERCP.

SECTION IV: RISK PREDICTION & PREVENTION

Section IV continues to focus on risk stratification within ERCP. In **chapter 7**, the aim was to assess the knowledge and preferences of Dutch endoscopists regarding prophylaxes and risk-factors for post-ERCP pancreatitis, and how this had changed over time after the publication of new recent guidelines. This will be assessed through two cross-sectional, nationwide surveys conducted with a seven-year interval.

As previously stated, preventing post-ERCP adverse events can be achieved by avoiding poorly indicated ERCPs without therapeutic benefit. As choledocholithiasis is the indication for ERCP in the majority of procedures, reducing the number of patients who undergo an unnecessary ERCP for the suspicion of choledocholithiasis could reduce the absolute number of post-ERCP adverse events. The ESGE guideline recommends the application of MRI or EUS in patients with an intermediate likelihood of choledocholithiasis.[58] In **chapter 8**, the clinical adherence to this guideline, in respect to whether additional imaging is performed, will be explored in a multi-center retrospective cohort.

SECTION V

Section V contains **chapters 9 and 10**, which will provide a summary of the findings in this thesis, discuss their place in the setting of the current body of literature, and elaborate on future directions.

REFERENCES

1. Langerhans P. Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse. Medizinische Fakultät. Berlin: Fiedrich-Wilhelms-Universität Berlin, 1869.
2. Von Mering I. Diabetes mellitus nach Pancreas extirpation. Zentral Klin. Medzin 1889;10:394.
3. Gley E. Diabète pancréatique expérimental. Essais de traitement. Ann. Soc. Med. Gand 1900;70:247-57.
4. Pavlov IP, Thompson WH. The work of the digestive glands : lectures by Professor J. P. Pawlow. London: C. Griffin, 1902.
5. Bernard C. Mémoire sur le pancréas et sur le rôle de suc pancréatique dans les phénomènes digestifs, particulièrement dans la digestion des matières grasses neutres: avec neuf planches gravées, en partie coloriées: J.-B. Baillière, 1856.
6. Harper AA, Raper HS. Pancreozymin, a stimulant of the secretion of pancreatic enzymes in extracts of the small intestine. J Physiol 1943;102:115-25.
7. Bayliss WM, Starling EH. The mechanism of pancreatic secretion. J Physiol 1902;28:325-53.
8. CINA Explorer: An interactive tool for quick access to key NAACCR cancer statistics based on the Cancer in North America (CiNA) dataset from the North American Association of Central Cancer Registries.
9. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer statistics, 2025. CA Cancer J Clin 2025;75:10-45.
10. Wood LD, Canto MI, Jaffee EM, et al. Pancreatic Cancer: Pathogenesis, Screening, Diagnosis, and Treatment. Gastroenterology 2022;163:386-402.e1.
11. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
12. Rahib L, Wehner MR, Matrisian LM, et al. Estimated Projection of US Cancer Incidence and Death to 2040. JAMA Network Open 2021;4:e214708-e214708.
13. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nature Reviews Gastroenterology & Hepatology 2021;18:493-502.
14. Chen J, Baithun SI. Morphological study of 391 cases of exocrine pancreatic tumours with special reference to the classification of exocrine pancreatic carcinoma. J Pathol 1985;146:17-29.
15. Morohoshi T, Held G, Klöppel G. Exocrine pancreatic tumours and their histological classification. A study based on 167 autopsy and 97 surgical cases. Histopathology 1983;7:645-61.
16. Miller JR, Baggenstoss AH, Comfort MW. Carcinoma of the pancreas. Effect of histological type and grade of malignancy on its behavior. Cancer 1951;4:233-241.
17. Singhi AD, Wood LD. Early detection of pancreatic cancer using DNA-based molecular approaches. Nat Rev Gastroenterol Hepatol 2021;18:457-468.

18. Pittman ME, Rao R, Hruban RH. Classification, Morphology, Molecular Pathogenesis, and Outcome of Premalignant Lesions of the Pancreas. Arch Pathol Lab Med 2017;141:1606-1614.

19. Omori Y, Ono Y, Tanino M, et al. Pathways of Progression From Intraductal Papillary Mucinous Neoplasm to Pancreatic Ductal Adenocarcinoma Based on Molecular Features. Gastroenterology 2019;156:647-661.e2.

20. Jang KT, Park SM, Basturk O, et al. Clinicopathologic characteristics of 29 invasive carcinomas arising in 178 pancreatic mucinous cystic neoplasms with ovarian-type stroma: implications for management and prognosis. Am J Surg Pathol 2015;39:179-87.

21. The European Study Group on Cystic Tumours of the P. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018;67:789.

22. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017;17:738-753.

23. Waddell N, Pajic M, Patch A-M, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 2015;518:495-501.

24. Smit VTHBM, Boot AJM, Smits AMM, et al. KRAS codon 12 mutations occur very frequently in pancreatic adenocarcinomas. Nucleic Acids Research 1988;16:7773-7782.

25. Almoguera C, Shibata D, Forrester K, et al. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell 1988;53:549-54.

26. Paniccia A, Polanco PM, Boone BA, et al. Prospective, Multi-Institutional, Real-Time Next-Generation Sequencing of Pancreatic Cyst Fluid Reveals Diverse Genomic Alterations That Improve the Clinical Management of Pancreatic Cysts. Gastroenterology 2023;164:117-133.e7.

27. Wu Y, Seufert I, Al-Shaheri FN, et al. DNA-methylation signature accurately differentiates pancreatic cancer from chronic pancreatitis in tissue and plasma. Gut 2023;72:2344-2353.

28. Network® NCC. NCCN Guidelines Pancreatic Adenocarcinoma v2.2025 2025.

29. Tirosh A, Journy N, Folio LR, et al. Cumulative Radiation Exposures from CT Screening and Surveillance Strategies for von Hippel-Lindau–associated Solid Pancreatic Tumors. Radiology 2019;290:116-124.

30. Canto MI, Hruban RH, Fishman EK, et al. Frequent Detection of Pancreatic Lesions in Asymptomatic High-Risk Individuals. Gastroenterology 2012;142:796-804.

31. Boekestijn B, Feshtali S, Vasen H, et al. Screening for pancreatic cancer in high-risk individuals using MRI: optimization of scan techniques to detect small lesions. Familial Cancer 2024;23:295-308.

32. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol 2004;2:606-21.

33. Agarwal B, Abu-Hamda E, Molke KL, et al. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. Am J Gastroenterol 2004;99:844-50.

34. Becker CD. ESR Modern Radiology eBook: Pancreas and Spleen Imaging., 2025.

35. Chari ST. Detecting Early Pancreatic Cancer: Problems and Prospects. Seminars in Oncology 2007;34:284-294.

36. Klatte DCF, Boekestijn B, Onnekink AM, et al. Surveillance for pancreatic cancer in high-risk individuals leads to improved outcomes: a propensity score-matched analysis. Gastroenterology 2023.

37. Blackford AL, Canto MI, Klein AP, et al. Recent Trends in the Incidence and Survival of Stage 1A Pancreatic Cancer: A Surveillance, Epidemiology, and End Results Analysis. J Natl Cancer Inst 2020;112:1162-1169.

38. Yoon SH, Lee JM, Cho JY, et al. Small (≤20 mm) Pancreatic Adenocarcinomas: Analysis of Enhancement Patterns and Secondary Signs with Multiphasic Multidetector CT. Radiology 2011;259:442-452.

39. Klatte DCF, Boekestijn B, Wasser MNJM, et al. Pancreatic Cancer Surveillance in Carriers of a Germline CDKN2A Pathogenic Variant: Yield and Outcomes of a 20-Year Prospective Follow-Up. Journal of Clinical Oncology 2022:JCO.22.00194.

40. Overbeek KA, Levink IJM, Koopmann BDM, et al. Long-term yield of pancreatic cancer surveillance in high-risk individuals. Gut 2022;71:1152-1160.

41. Canto MI, Almario JA, Schulick RD, et al. Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance. Gastroenterology 2018;155:740-751.e2.

42. Chhoda A, Vodusek Z, Wattamwar K, et al. Late-Stage Pancreatic Cancer Detected During High-Risk Individual Surveillance: A Systematic Review and Meta-Analysis. Gastroenterology 2022;162:786-798.

43. Early DS, Acosta RD, Chandrasekhara V, et al. Adverse events associated with EUS and EUS with FNA. Gastrointestinal Endoscopy 2013;77:839-843.

44. Akshintala VS, Kanthasamy K, Bhullar FA, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: an updated systematic review and meta-analysis of 145 randomized controlled trials. Gastrointest Endosc 2023;98:1-6.e12.

45. Bishay K, Meng ZW, Khan R, et al. Adverse Events Associated With Endoscopic Retrograde Cholangiopancreatography: Systematic Review and Meta-Analysis. Gastroenterology 2025;168:568-586.

46. Pezzilli R, Romboli E, Campana D, et al. Mechanisms Involved in the Onset of Post-ERCP Pancreatitis. JOP : Journal of the pancreas 2002;3:162-8.

47. Johnson GK, Geenen JE, Johanson JF, et al. Evaluation of post-ERCP pancreatitis: potential causes noted during controlled study of differing contrast media. Gastrointestinal Endoscopy 1997;46:217-222.

48. Fazel A, Quadri A, Catalano MF, et al. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. Gastrointest Endosc 2003;57:291-4.

49. Dumonceau JM, Kapral C, Aabakken L, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2020;52:127-149.

50. Kusterer K, Enghofer M, Zendler S, et al. Microcirculatory changes in sodium taurocholate-induced pancreatitis in rats. American Journal of Physiology-Gastrointestinal and Liver Physiology 1991;260:G346-G351.

51. Buxbaum J, Yan A, Yeh K, et al. Aggressive hydration with lactated Ringer's solution reduces pancreatitis after endoscopic retrograde cholangiopancreatography. Clin Gastroenterol Hepatol 2014;12:303-7.e1.

52. Gross S, Trautwein C, Behrens A. Computer-based classification of small colorectal polyps by using narrow-band imaging with optical magnification. Gastrointest Endosc 2011;74:1354-1359.

53. Mäkelä A, Kuusi T, Schröder T. Inhibition of serum phospholipase-A2 in acute pancreatitis by pharmacological agents in vitro. Scand J Clin Lab Invest 1997;57:401-7.

54. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012;366:1414-22.

55. Goldberg-Stein S, Frigini LA, Long S, et al. ACR RADPEER Committee White Paper with 2016 Updates: Revised Scoring System, New Classifications, Self-Review, and Subspecialized Reports. J Am Coll Radiol 2017;14:1080-1086.

56. Kemppainen E, Hedström J, Puolakkainen P, et al. Urinary trypsinogen-2 test strip in detecting ERCP-induced pancreatitis. Endoscopy 1997;29:247-51.

57. Jeurnink SM, Siersema PD, Steyerberg EW, et al. Predictors of complications after endoscopic retrograde cholangiopancreatography: a prognostic model for early discharge. Surg Endosc 2011;25:2892-900.

58. Manes G, Paspatis G, Aabakken L, et al. Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2019;51:472-491.